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Accessing Grignard Reluctant Aldehyde in 2-Oxoaldehyde by Organocuprates to Give [1,2] Addition and Oxidative Coupling Reactions

Satyanarayana Battula,* Aman A. Desai, Jigar Y. Soni, and Dhruv P. Mehta

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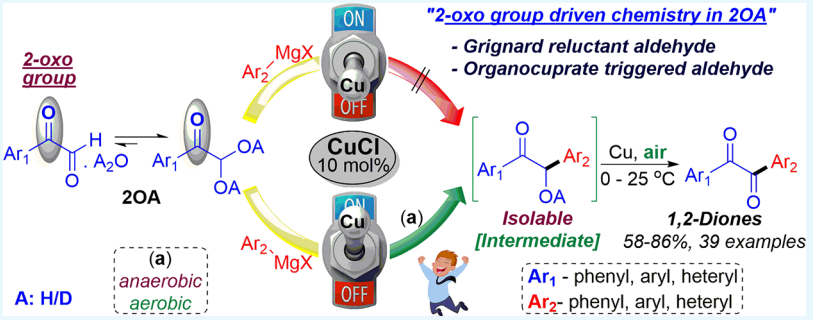

ABSTRACT: Novel finding of aldehyde in 2-oxoaldehyde (2OA) is presented as it unprecedentedly disinclines to react with Grignard reagents but reacts with moderate organocuprate reagents in anaerobic condition to give [1,2] addition (α-hydroxyketones) reaction. In the presence of air, the reaction produces an efficient protocol for the synthesis of 1,2-diones through a copper-catalyzed oxidative cross-coupling reaction at room temperature. Mechanistic studies indicate that α-hydroxy ketone perhaps is generated before the hydrolysis step/acid work-up process. The α-keto group of 2OA causes to exhibit this peculiar aldehyde behavior toward these organometallic reagents.

INTRODUCTION

After the discovery of Grignard reagent in 1900,[1] its incredible applicability with carbonyls for the generation of magnesium alcolates/alcohols (on hydrolysis) is very well conversant and has undoubtedly been used extensively for decades.[2,3] However, Grignard reagents exhibit a robust reactivity profile with carbonyl compounds but may associate with a few exceptions of side reactions based on the nature of groups at its carbonyl carbon. Its reactions with ketones suffer from various competing side reactions like β-hydride elimination, enolizations, reduction, and others,[4] but generally aldehydes have no such limitations in its Grignard reactions. The reactivities of Grignard reagents with various aldehydes of different chemical environments have been explored well. As we know, α,β-unsaturated aldehydes/conjugated aldehydes and aldehydes with α-C-H hydrogens react with Grignard reagents (RMgX) to undergo (1,2)-nucleophilic addition reactions to generate secondary alcohols on hydrolysis (Figure 1a); in addition, the second one perhaps generates RH in minute quantities through self-enolization, whereas Grignard reagents are strongly basic.

So far, as we know, no Grignard reaction has been reported with aldehyde while in the presence of the α/2-oxo group environment [2-oxoaldehyde (2OA)].

The reactions of 2OA are unique by its distinctive reactivity[5−7] as its aldehyde with higher electrophilicity, rather than regular aldehyde, owing to the existence of the electron-withdrawing 2-oxo group, offers a decisive chemical environment leading to various intriguing chemical reactions to multiple C−X bonds[6] (e.g., amine mediated cross couplings with various nucleophiles instead of Mannish & Petasis reaction;[6a,b] catalyst-free hydrophosphonylation,[6d] phosphonate-phosphate/phosphine oxide-phosphinate rearrangement,[6e] and others) and functionalized heterocycles[7] unlike the usual aldehydes. In the present context, while we tried with Grignard nucleophiles, the aldehyde in 2OA surprisingly shows reluctance to react (Figure 1b). Therefore, we design a strategy to make this reaction successful through using moderate-to-mild organometallic reagents (*in situ* preparation from Grignard) instead of strong Grignard reagents to obtain corresponding α/2-ketols (Scheme 1), wherein we accomplish

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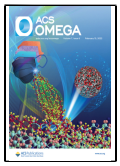


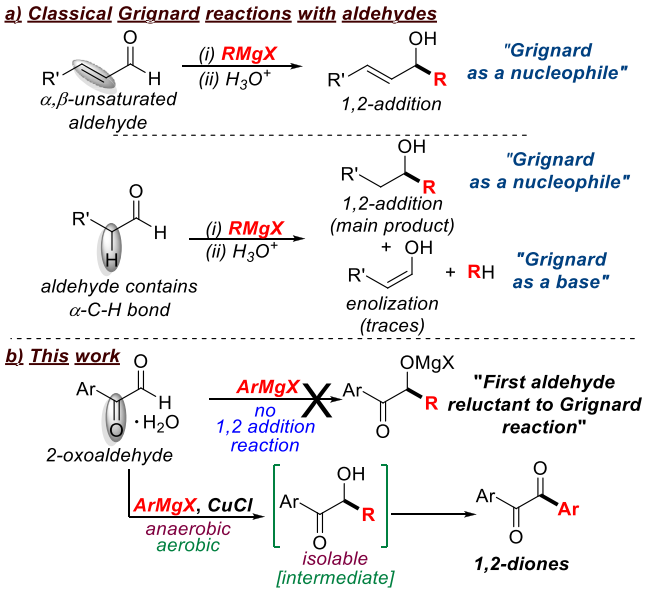
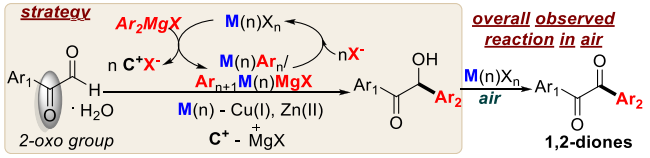


Figure 1. General protocols of Grignard reactions with aldehyde.

Scheme 1. Strategy for the Synthesis of α/2-Ketols

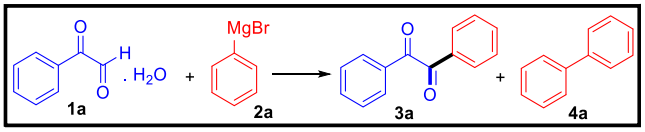


the synthetic protocol for 1,2-diones in atmospheric air through the formation of α/2-ketols (product in anaerobic condition) by a copper-catalyzed oxidative coupling reaction of 2OAs with Grignard reagents at room temperature.

RESULTS AND DISCUSSION

We began our study by conducting a model reaction between 1 equiv of phenylglyoxal **1a** in toluene with phenyl magnesium bromide **2a** (1.1 equiv) in tetrahydrofuran (THF) and a catalytic amount of CuCl (10 mol %) at −20 to 5 °C under an inert atmosphere (N_2/Ar). To our delight, we isolated 23% of benzil **3a** along with a small amount of biphenyl **4a** (entry 1; Table 1). With this inspiring result, we conducted few more reactions by increasing the amount of Grignard reagent (entry 2−4) at 0−5 °C, wherein we generated 67% of **3a** with 1.5 equiv of Grignard reagent **2a** (entry 4). Later, the reaction was allowed to continue at 25 °C after the addition of 1.5 equiv of PhMgBr **2a** at 0−5 °C (entry 5), which could improve the reaction yield to 71%. Once again, we used higher amounts of **2a** to study the reaction at the same temperatures (entry 6, 7), and the yield of **3a** increased to 76%. Next, we tested the reaction by allowing it in the air at 25 °C after the addition of **2a** to **1a**, and 79% of **3a** was generated without the formation of homo coupling product **4a** (entry 8). In addition, no improvement in the yield was observed when the reaction was performed completely at 25 °C along with the addition temperature of Grignard **2a** to **1a** (entry 9). Further, we screened the reaction for different catalytic amounts (entry 10 and 11), but higher yields were not generated. Later, we screened the reaction with various copper catalysts to make the reaction more efficient (entry 12−15), and unfortunately better yields were not generated. We also found that

Table 1. Optimization Studies of the Reaction[a]



entry	PhMgBr (equiv)	catalyst (mol %)	temp (°C) t_a	temp (°C) t_r	time (h)	yield (%) 3a	yield (%) 4a
1[b]	1.1	CuCl (10)	−20	0−5	6	23	<5
2[b]	1.2	CuCl (10)	0−5	0−5	6	51	<5
3[b]	1.3	CuCl (10)	0−5	0−5	6	62	<5
4[b]	1.5	CuCl (10)	0−5	0−5	6	67	<5
5[b]	1.5	CuCl (10)	0−5	25	4	71	<5
6[b]	1.8	CuCl (10)	0−5	25	3	76	<5
7[b]	2.0	CuCl (10)	0−5	25	3	76	>5
8	**1.8**	**CuCl** (10)	0−5	**25**	**3**	79	–
9	1.8	CuCl (10)	25	25	3	66	>5
10	1.8	CuCl (5)	0−5	25	3	69	<5
11	1.8	CuCl (15)	0−5	25	3	78	>5
12	1.8	CuI (10)	0−5	25	3	24	<5
13	1.8	CuBr (10)	0−5	25	3	27	<5
14	1.8	CuCl2 (10)	0−5	25	3	18	10
15	1.8	Cu(OAc)2 (10)	0−5	25	3	32	<5
16	1.8	pyrrolidine (10)	0−5	25	10	nr	–
17[c]	1.8	CuCl (10)	0−5	25	10	38	15
18[d]	1.8	CuCl (10)	0−5	25	10	42	10

[a]Reaction conditions: **1a** (1 equiv), **2a** (1.8 equiv) in toluene & THF solvent mixture for 3 h. [b]Under inert atmosphere (N_2/Ar), rest of the reactions in air (N_2 atmosphere used for Grignard addition); t_a—addition temperature of **2a** to **1a** and t_r—reaction temperature. [c]Reaction was conducted in toluene solvent. [d]Reaction was conducted in THF solvent; nr—no reaction.

pyrrolidine would not be the choice to catalyze the reaction, wherein product **3a** was not observed (entry 16). However, two more reactions were performed in toluene and THF solvents solely (entry 17 and 18), but these reactions failed to produce better results.

With the optimized procedure in hand, we explored the scope of the reaction by treating phenyl glyoxal **1a** with various substituted phenyl and naphthyl Grignard reagents **2** (Scheme 2). As observed, irrespective of substitution on the phenyl ring, all phenyl-based Grignard reagents are compatible to the reaction conditions and smoothly converted to the corresponding 1,2-diones with moderate-to-excellent yields. Based on our observation, the Grignard reagents bearing electron-donating groups gave relatively more yields than the Grignard with electron-withdrawing groups. In addition, the reaction with naphthyl-based Grignard reagent also produced appreciable yield for **3j**. The reaction with the benzyl Grignard reagent could not obtain the corresponding 1,2-dione product. A few reactions were done with both bromo- and chloro-based Grignard reagents to check their viability to the reaction. Among these, bromo Grignard reagents produced higher yields than chloro Grignard reagents.

The scope of the reaction was further extended in terms of multiple reactions, which were performed between various 2OAs **1** and a variety of Grignard reagents **2** (Scheme 3). As observed, all reactions were effortlessly converted to the

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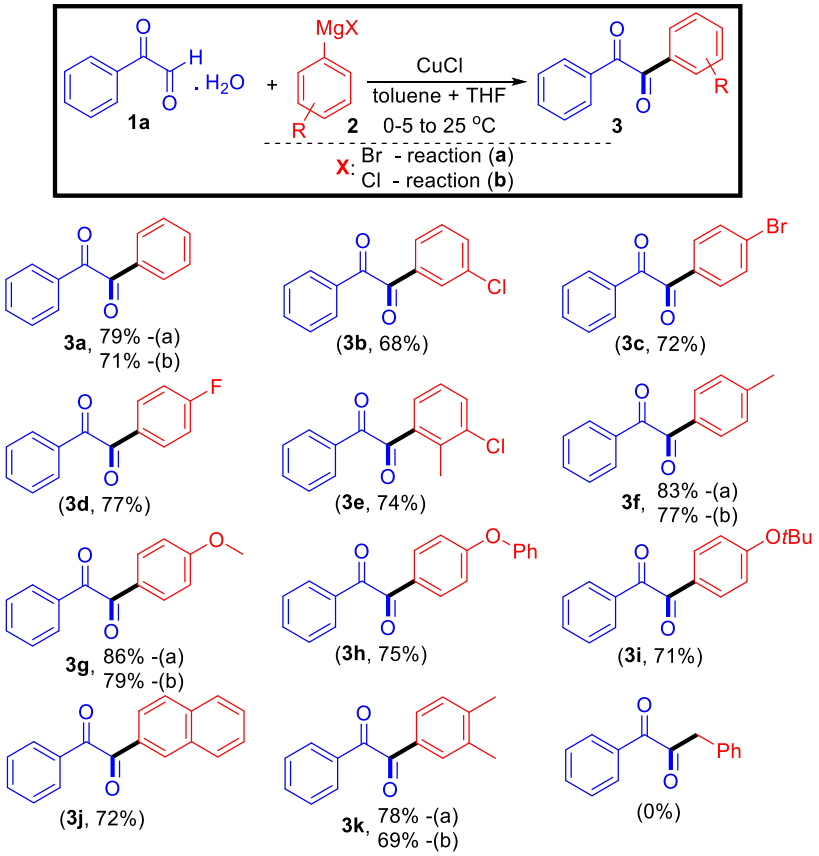
Scheme 2. Scope of the Reaction[a]



[a]Reaction conditions: **1a** (1 equiv), **2a** (1.8 equiv), and CuCl (10 mol %); N_2 atmosphere for Grignard addition, air environment was used after addition; toluene & THF solvent mixture; 0−5 °C to rt, 3−6 h. Both Grignard reactions (**a**) & (**b**); unspecified reactions generated from reaction (**a**).

products with moderate-to-appreciable yields. In general, electron-donating groups on both 2OA and Grignard could cause to produce more yields compared to the analogous reagents with electron-withdrawing groups. Naphthyl and hetaryl oxoaldehydes were compatible to the reaction conditions and produced good yields. Aliphatic Grignard reagents were found to be ineffective to the reaction (ethyl and benzyl Grignard's) and could not obtain their corresponding diones. In addition, few dione products (**3l**, **3m**, **3s**, **3t**, and **3z**) and their yields were observed by cross over of the substrates [processes (**a**) & (**b**)] and found to be comparable in productivity in both the processes.

To investigate the reaction mechanism, we studied few controlled experiments between phenylglyoxal **1a** and phenyl magnesium bromide **2a** (Scheme 4). In experiment (**1**), the reaction was verified by treating **1a** and **2a** with LiCl (20 mol %) as the catalyst accelerator along with CuCl,[8] but the reaction results proved that CuCl solely gave better results. Later, to check the requirement of mildness of organo-nucleophile (experiment **2**), we treated the reaction with $ZnCl_2$ (organozinc),[9] wherein we observed a lower yield of product **3a**. Further, to check the efficiency of oxidation, we treated the reaction of **1a** and **2a** at optimized conditions under an argon atmosphere (experiment **3**), and **3a** was generated with 55% yield. It explains that the oxidation was ensued by dissolved oxygen. In another experiment (**4**), while using atmospheric air in the reaction, improved yield of **3a** (79%) was observed (no yield of **4a**, Table 1; entry 8), and it emphasized the importance of air oxygen to this reaction. In addition, we conducted one more reaction (experiment **5**) under an O_2 balloon; the results notified that additional O_2 was not supported by further enrichment of the yield of **3a**; instead it produced more amount of homo coupling product of Grignard reagent **4a** (11%). It clearly indicated that air oxygen is adequate to trigger the reaction. Furthermore, to confirm the reaction pathway, the reaction was being studied in complete absence of air oxygen by degassing the dissolved oxygen from the solvent through N_2 purging followed by sonication under reduced pressure. Under these conditions, experiments **6** & **7** produced α-ketols **5a** (90%) and **5b** (93%), respectively, in appreciable yields, and their corresponding benzils were procured in minute quantities. These results clearly indicates that the reaction proceeds through the formation of α-ketol. Additionally, to add more strength to the mechanism, benzoin **5a** was treated under the optimized reaction conditions (experiment 8), benzil **3a** (92%) was produced in appreciable yield. More interestingly, benzoin **5a** formation was not observed in a reaction (experiment 9), wherein the catalyst was completely absent. It clearly indicates the role of copper in the reaction as it not only catalyzes the oxidation of ketol **5a** but also exerts a novel role in the reaction of Grignard nucleophile with the aldehyde of 2OA. With this insight, to investigate the unique nature of the aldehyde of 2OA in this reaction, we conducted an experiment (10) between benzaldehyde **6a** and phenyl magnesium bromide **2a** under optimized conditions. In the absence of a catalyst, we were able to procure diphenyl

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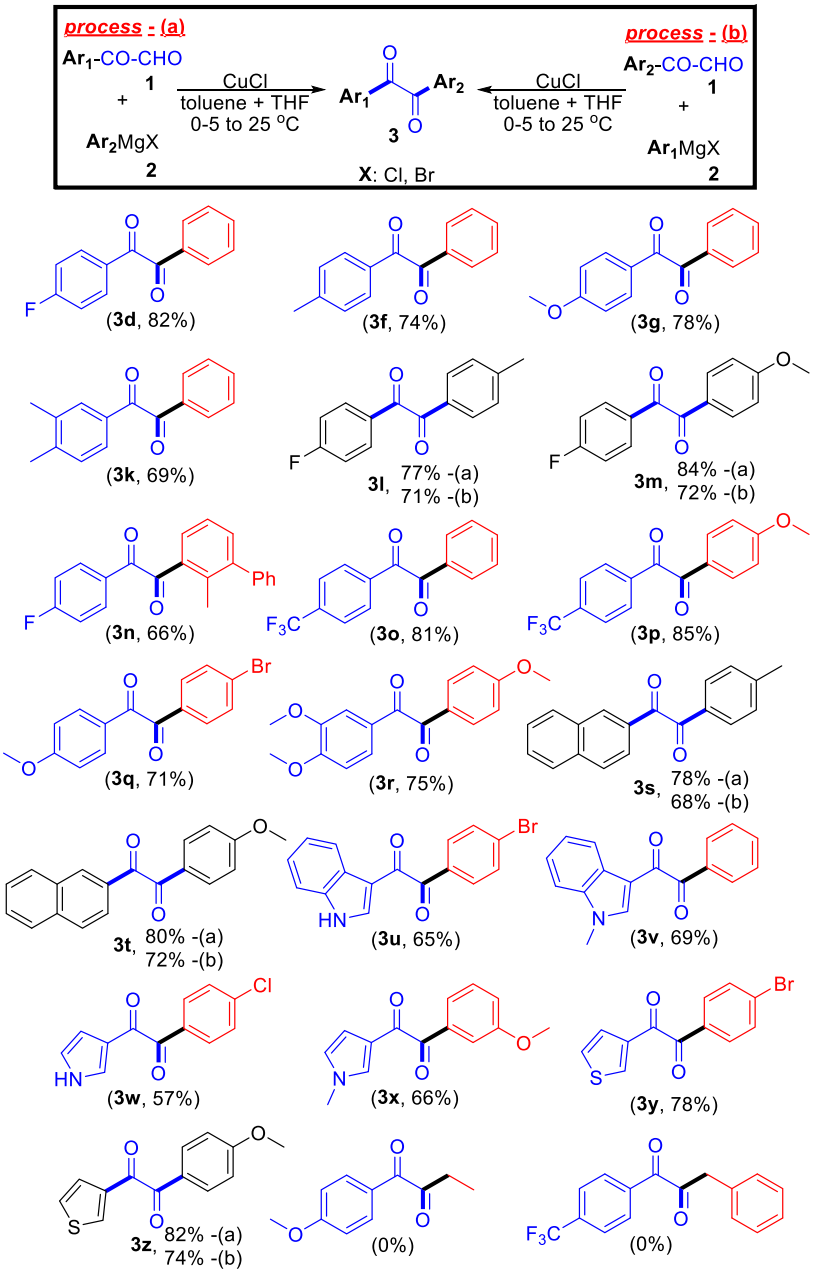
Scheme 3. Scope of the Reaction[a]



[a]Reaction conditions: **1** (1 equiv), **2** (1.8 equiv), and CuCl (10 mol %); N_2 atmosphere for Grignard addition, air environment used after addition; toluene & THF solvent mixture; 0−5 °C to rt, 3−6 h; few reaction yields observed by both process (**a**) & (**b**). Unspecified reaction yields given by only process (**a**).

methanol **7a** (89%) only. The same reaction when performed in the presence of a catalyst could produce benzophenone **8a** (oxidation of **7a** by CuCl) along with **7a**.

Further to the reaction mechanism, we prepared phenylglyoxal·D_2O **9** (D_2O crystallized with PG) and performed its reaction with phenyl magnesium bromide **2a** under the reaction conditions of experiment (6). The reaction produced benzoin-OD **10** in 90% yield (Figure 2a). The formation of benzoin-OD **10** was confirmed by ^{1}H NMR spectra, in which it shows low integrations for the α-C-H and alcoholic protons (compared to **5a**; Figure 2b,c) as the deuterium atom migrates between these two positions in both benzoin-OD **10** tautomeric forms (Figure 2d). The generation of benzoin-OD clearly indicates that the alcoholic hydrogen in the benzoin arises from the crystallized water of phenylglyoxal. It further confirms that the 2OAs/phenylglyoxals directly produce alcohols instead of alcolates while reacting with Grignard reagents under the said optimized reaction conditions.

On the basis of previous literature and controlled experiments, the possible reaction mechanism is described in Scheme 5. The Grignard reagent initially produces typically unreactive/very low reactive organocopper reagent **A** with CuCl, and it further reacts with Grignard reagent (as it uses in excess quantity) and generates highly nucleophilic organomagnesium homocuprate **B** through transmetalation of magnesium with copper.[10] This **B** attacks on the aldehyde of 2OA which is crystallized with H_2O molecule to generate α-ketol **5**. In the

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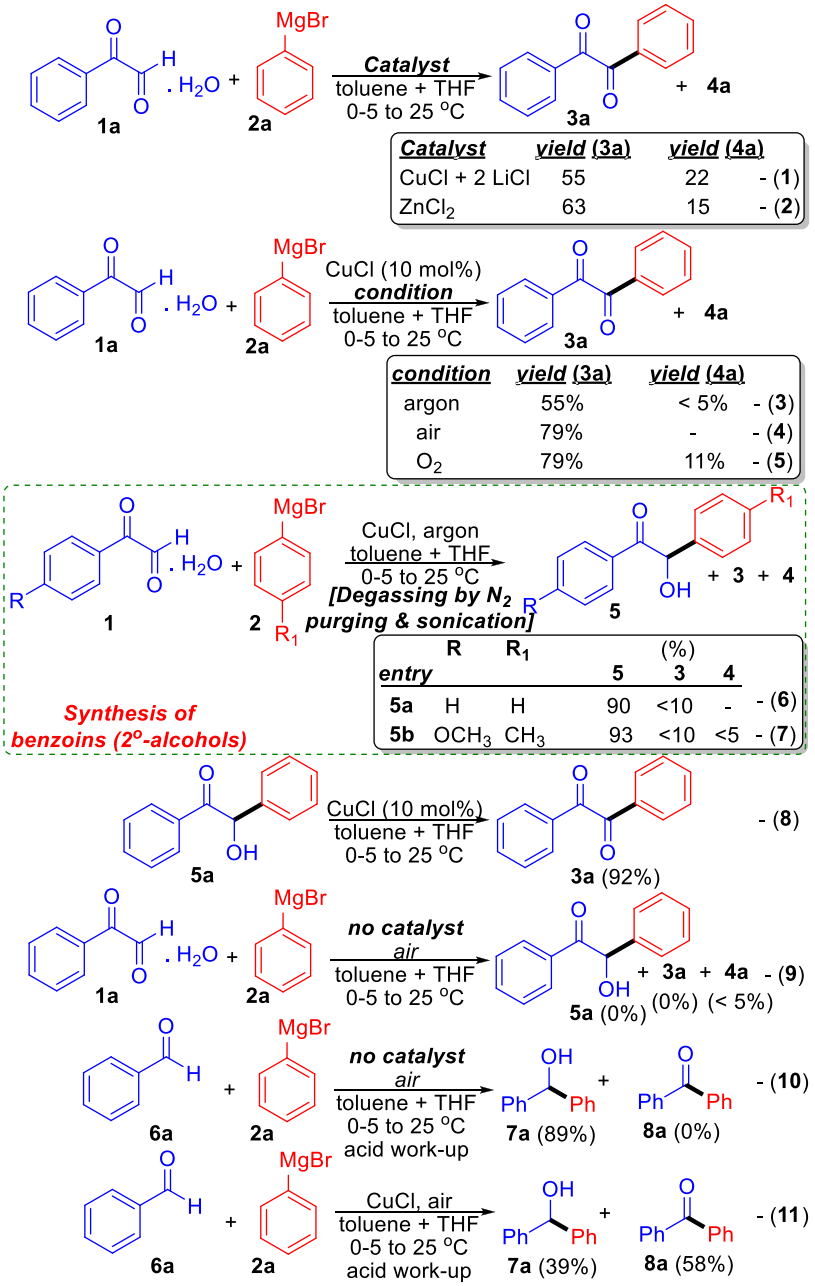
Scheme 4. Controlled Experiments



absence of air (anerobic conditions), α-ketol could be the final product as it does not undergo oxidation reaction.However, in the presence of air, α-ketol **5** would be an intermediate and further undergoes Cu-mediated oxidation[11] and produces benzil **3**. The formation of biphenyl **4** perhaps could be explained through the homocoupling of Grignard reagents in the presence of Cu catalyst and air.[12]

CONCLUSIONS

In summary, we have identified a unique nature of aldehyde in 2OA as it displays reluctancy to react with Grignard reagent and react with organomagnesium cuprate to generate α-ketols in anerobic condition, and that undergoes Cu(I)-mediated oxidation to generate benzils in the presence of air. This reaction produced alcohols before the hydrolysis reaction. The 2-oxo/keto group of 2OA causes the novel reactivity of aldehyde toward organometallics. This reaction can tolerate a wide variety of substrate scope with respect to both 2OA and Grignard reagents. Aliphatic Grignard reagent is found to be not obeying this reaction. Further studies of 2OA of distinctive nature are in progress.

EXPERIMENTAL SECTION

General. All chemicals were obtained from Sigma-Aldrich, TCI Chemicals, and Alfa-Aesar company and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker-AVANCE Neo Nanobay FT-NMR 400 MHz instrument. Chemical shifts for protons are reported in parts per million (ppm) downfield from tetramethyl silane and are referenced to the residual proton in the NMR solvents ($CDCl_3$, DMSO-d_6: 7.26, 2.52 ppm). Carbon nuclear magnetic resonance (^{13}C NMR solvents $CDCl_3$; DMSO-d_6: 77.0; 39.5 ppm) spectra

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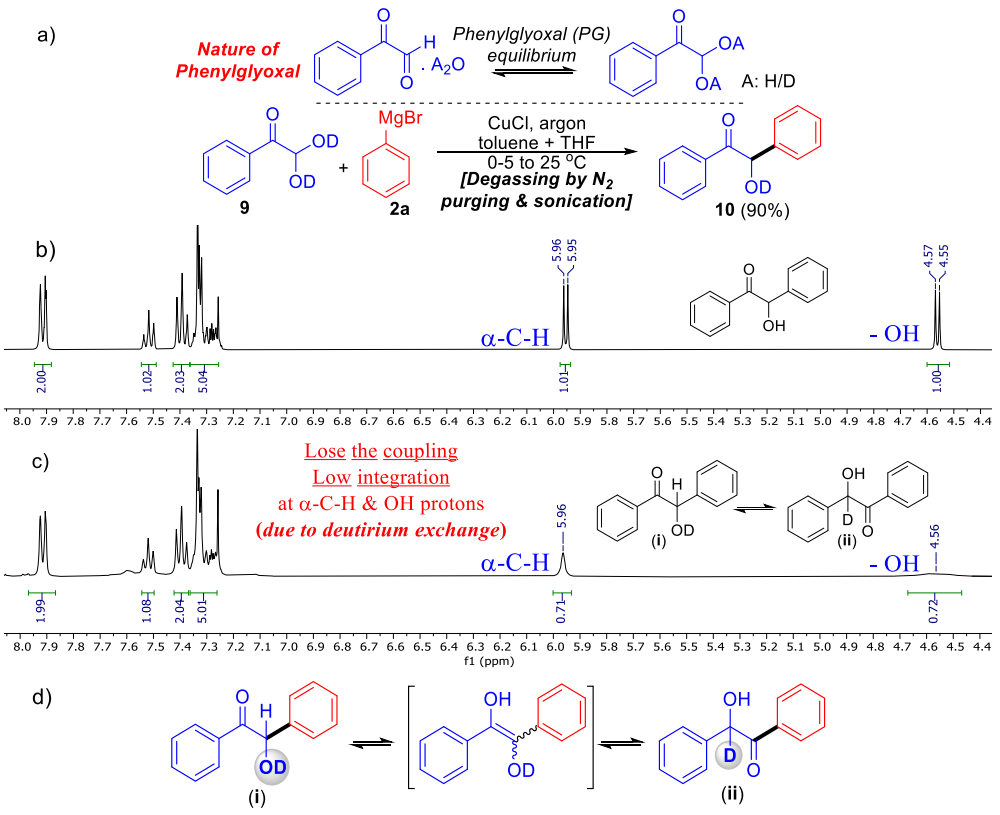
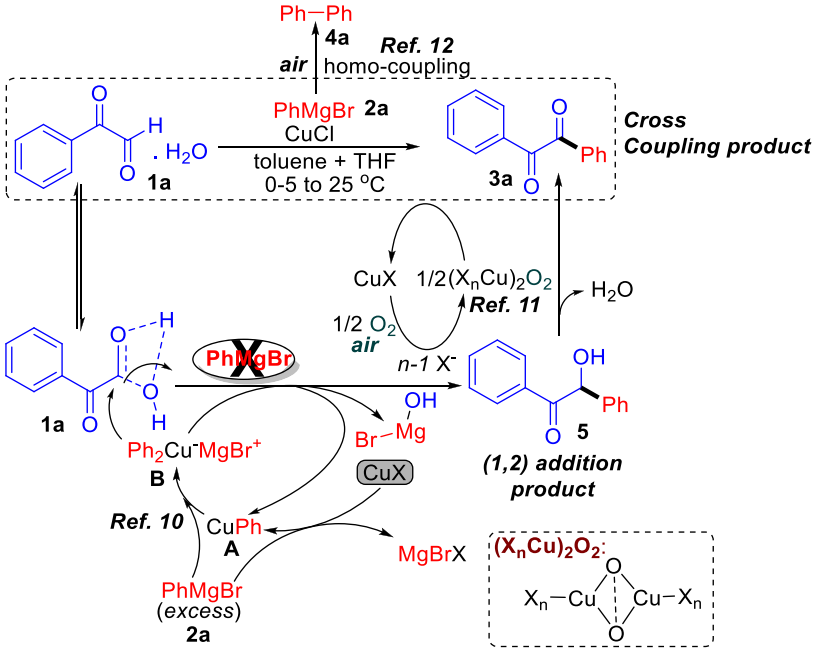


Figure 2. (a) Reaction of crystalized phenylglyoxal·D_2O **9** and phenyl magnesium bromide **2a**; (b) ^{1}H NMR spectra of benzoin; (c) ^{1}H NMR spectra of benzoin-OD [mixture of (**i**) & (**ii**)]; (d) tautomerization of benzoin-OD.

Scheme 5. Plausible Reaction Mechanism



were recorded at 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethyl silane and are referenced to the carbon resonance of the solvent. Mass spectra of compounds were recorded with an Agilent 5977A MSD GC−MS instrument. IR spectra were recorded on an Agilent Cary 630 FT-IR spectrophotometer.

Procedure for the Preparation of 1,2-Diones (3a−3z). The reaction was carried out in a two-necked round-bottom flask under a N_2 inert atmosphere, and 10 mol % CuCl was added. Substituted 2OA **1** (0.66 mmol) in dry toluene was subjected to the reaction, and later 1.8 equiv of Grignard reagent **2** in dry THF was added slowly through a dropping funnel for 5 to 10 min at 5 °C. After complete addition of the

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Grignard reagent, the reaction mixture was allowed to stir at room temperature for 3 h in the air by removing the inert atmosphere. The reaction status was checked with TLC, and after its completion, excess Grignard was quenched and the reaction mass was extracted in ethyl acetate. The crude was purified by column chromatography by using silica gel (#100−200) and ethyl acetate in hexane (5:95) as an eluent.

Procedure for the Preparation of 5a and 5b [Experiments (6 & 7)]. The reaction was carried out in a 50 mL two-necked round-bottom flask under a N_2 inert atmosphere, and 10 mol % CuCl was added. 2OA **1** (0.66 mmol) in dry toluene was subjected to the reaction, and removal of the dissolved oxygen in the reaction solvent was done by nitrogen purging followed by sonication under reduced pressure. 1.8 equiv of Grignard reagent **2** in dry THF (removal of the dissolved oxygen was performed) was added slowly through a dropping funnel for 5 to 10 min at 0−5 °C. After complete addition of the Grignard reagent and continued N_2 purging, the reaction mixture was allowed to stir at room temperature for 3 h. The reaction status was checked with TLC, and after its completion, excess Grignard was quenched by dil. HCl and the reaction mass was extracted in ethyl acetate. The crude was purified by column chromatography by using silica gel (#100−200) and ethyl acetate in *n*-hexane (5:95) as an eluent.

*Benzil (**3a**).*[13a] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.95 (m, 4H), 7.66 (t, J = 7.4 Hz, 2H), 7.52 (t, J = 7.7 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.62, 134.94, 132.98, 129.94, 129.05; GC−MS (EI) $m\backslash z$ (relative intensity): 210.0 (M^+, 7), 105.1 (100), 77.1 (54), 51.1 (15).

*1-(3-Chlorophenyl)-2-phenylethane-1,2-dione (**3b**).*[13b] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.94 (m, 3H), 7.84 (d, J = 7.8 Hz, 1H), 7.71−7.60 (m, 2H), 7.53 (t, J = 7.8 Hz, 2H), 7.46 (t, J = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.58, 192.93, 135.46, 135.10, 134.75, 134.57, 132.74, 130.34, 129.97, 129.58, 129.10, 128.11; GC MS (EI) $m\backslash z$ (relative intensity): 244.0 (M^+, 0.1), 209.1 (2.1), 139.1 (17), 105.1 (100), 77.1 (19), 51.1 (5).

*1-(4-Bromophenyl)-2-phenylethane-1,2-dione (**3c**).*[13a] Yellow solid (176 mg, 82%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (dd, J = 8.3, 1.1 Hz, 2H), 7.87−7.82 (m, 2H), 7.70−7.64 (m, 3H), 7.53 (t, J = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.90, 193.34, 135.14, 132.74, 132.47, 131.72, 131.28, 130.56, 129.99, 129.12; GC−MS (EI) $m\backslash z$ (relative intensity): 287.9 (M^+, 1.3), 209.1 (4.3), 183.1 (26), 155.1 (10), 105.2 (100), 77.1 (46), 51.1 (12).

*1-(4-Fluorophenyl)-2-phenylethane-1,2-dione (**3d**).*[13b] Yellow solid (142 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−7.94 (m, 4H), 7.70−7.64 (m, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.23−7.14 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.07, 192.73, 168.08, 165.52, 135.00, 132.88, 132.79, 132.69, 129.94, 129.52, 129.07, 116.51, 116.29; GC−MS (EI) $m\backslash z$ (relative intensity): 228.1 (M^+, 4.4), 123.1 (48.1), 105.2 (100), 95.2 (23.4), 77.2 (42.3), 75.2 (13.1), 51.1 (14.8).

*1-(3-Chloro-2-methylphenyl)-2-phenylethane-1,2-dione (**3e**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02−7.96 (m, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.57−7.50 (m, 3H), 7.22 (t, J = 7.9 Hz, 1H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.73, 193.81, 138.29, 137.02, 134.88, 134.51, 134.25, 132.78, 130.76, 129.98, 129.07, 126.68, 17.36. GC−MS (EI) $m\backslash z$ (relative intensity): 257.8 (M^+,0), 154.8 (32.2), 126.9 (10.8), 104.9 (100), 76.9 (56), 62.9 (15.1), 50.9 (22.9).

*1-Phenyl-2-(p-tolyl)ethane-1,2-dione (**3f**).*[13a] Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, J = 8.2, 1.1 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 7.69−7.63 (m, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H). GC−MS (EI) $m\backslash z$ (relative intensity): 224.1 (M^+, 0.1), 119.1 (100), 105 (20.5), 91.1 (30.5), 77.1 (24.2), 65 (8.1), 51.1 (4.1), 40.1 (3.54).

*1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione (**3g**).*[13a] Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (t, J = 8.5 Hz, 4H), 7.65 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H). GC−MS (EI) $m\backslash z$ (relative intensity): 240.1 (M^+, 4.4), 135.1 (100), 105.1 (14.1), 92.1 (19.2), 77.1 (49.3), 64.1 (11.0), 51.1 (14.9)

*1-(4-Phenoxyphenyl)-2-phenylethane-1,2-dione (**3h**).*[13c] Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.91 (m, 4H), 7.67−7.60 (m, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.43−7.36 (m, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.07 (dd, J = 8.6, 1.0 Hz, 2H), 7.04−6.99 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.69, 193.15, 163.72, 154.82, 134.89, 133.07, 132.41, 130.23, 129.95, 129.04, 127.44, 125.18, 120.55, 117.46; GC−MS (EI) $m\backslash z$ (relative intensity): 302 (M^+, 0), 198.2 (13.8), 197.2 (100), 169.3 (4.1), 141.3 (17.8), 115.2 (17.3), 105.3 (3.8), 77.2 (7.1), 51.0 (4.7).

*1-(4-(tert-Butoxy)phenyl)-2-phenylethane-1,2-dione (**3i**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01−7.96 (m, 2H), 7.92−7.88 (m, 2H), 7.67−7.62 (m, 1H), 7.51 (dd, J = 10.8, 4.7 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.82, 192.33, 161.31, 133.70, 132.16, 130.65, 128.91, 127.93, 125.98, 120.84, 79.21, 27.89. GC−MS (EI) $m\backslash z$ (relative intensity): 282.9 (M^+, 0), 185.9 (100), 156.9 (7.95), 139 (5.85), 127.9 (4.17), 57 (9.15), 44 (6.37), 41 (8.86), 51.0 (4.7).

*1-(Naphthalen-2-yl)-2-phenylethane-1,2-dione (**3j**).*[13d] Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.10 (dd, J = 8.6, 1.6 Hz, 1H), 8.06−8.00 (m, 2H), 7.97 (d, J = 8.7 Hz, 1H), 7.91 (t, J = 8.0 Hz, 2H), 7.70−7.62 (m, 2H), 7.55 (ddd, J = 12.3, 9.6, 4.3 Hz, 3H). GC−MS (EI) $m\backslash z$ (relative intensity): 260.1 (M^+, 0), 154.5 (17.1), 128.2 (32.2), 127.2 (100), 74.1 (16.8), 39.3 (19.7).

*1-(3,4-Dimethylphenyl)-2-phenylethane-1,2-dione (**3k**).*[13e] Yellow liquid (142 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00−7.93 (m, 2H), 7.74 (s, 1H), 7.72−7.61 (m, 2H), 7.50 (t, J = 7.7 Hz, 2H), 7.28−7.23 (m, 1H), 2.34 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.94, 194.69, 145.12, 137.66, 134.78, 133.14, 130.93, 130.78, 130.31, 129.93, 128.99, 127.80, 20.36, 19.75; GC−MS (EI) $m\backslash z$ (relative intensity): 238.1 (M^+, 3.2), 133.2 (100), 105.2 (40), 77.1 (26), 51.1 (26).

*1-(4-Fluorophenyl)-2-(p-tolyl)ethane-1,2-dione (**3l**).* Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05−7.98 (m, 1H), 7.89−7.79 (m, 2H), 7.69 (d, J = 8.1 Hz, 1H), 7.30 (dd, J = 10.8, 8.2 Hz, 2H), 7.21−7.12 (m, 2H), 2.44 (s, 3H). GC−MS (EI) $m\backslash z$ (relative intensity): 242 (M^+, 0), 123.2 (17.1), 119.2 (100), 95.2 (13.8), 75.2 (5.9), 65.2 (11.1), 51.2 (1.75).

*1-(4-Fluorophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**3m**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05−7.99 (m, 2H), 7.97−7.92 (m, 2H), 7.18 (t, J = 8.6 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H). GC−MS (EI) $m\backslash z$ (relative intensity): 258.1 (M^+, 0), 135.1 (100), 123.1 (14.1), 107.1 (10), 95.0 (17.1), 75.1 (13), 64.1 (8.0).

*1-(4-Fluorophenyl)-2-(2-methyl-[1,1′-biphenyl]-3-yl)-ethane-1,2-dione (**3n**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.04 (m, 2H), 7.61 (dd, J = 7.7, 0.8 Hz, 1H),

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7.50−7.40 (m, 4H), 7.31 (dd, J = 7.4, 5.8 Hz, 3H), 7.22 (t, J = 8.6 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.50, 192.93, 167.94, 165.37, 144.71, 140.72, 138.41, 135.35, 132.97, 132.84, 132.74, 131.89, 129.58, 129.28, 128.29, 127.38, 125.54, 116.50, 116.28, 18.75. GC−MS (EI) $m\backslash z$ (relative intensity): 318.3 (M^+, 0), 195.3 (100), 167.2 (20.6), 152.2 (39.6), 123.2 (23.6), 95.2 (23.0), 75.2 (10.4), 40.1 (19.4).

*1-Phenyl-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (**3o**).*[13a] Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 7.9 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.52, 193.08, 136.03, 135.77, 135.59, 135.31, 132.58, 130.26, 130.02, 129.19, 126.10, 126.07; GC−MS (EI) $m\backslash z$ (relative intensity): 278.0 (M^+, 0.3), 173.0 (15), 145.1 (24), 105.1 (100), 77.1 (43), 51.1 (43).

*1-(4-Methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-ethane-1,2-dione (**3p**).* Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.00−7.95 (m, 2H), 7.90 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.03−6.97 (m, 2H), 3.91 (s, 3H). GC−MS (EI) $m\backslash z$ (relative intensity): 308.1 (M^+, 0.1), 173.1 (10.2), 145.1 (22.2), 135.1 (100), 107.1 (13.6), 77.1 (25.7), 64.1 (12.3)

*1-(4-Bromophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**3q**).*[13f] Yellow solid (213 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.9 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.58, 192.41, 165.16, 132.47, 132.37, 131.97, 131.27, 130.29, 125.86, 114.45, 55.74; GC MS (EI) $m\backslash z$ (relative intensity): 318 (M^+, 0.1), 183.1 (21), 155.1 (3.7), 135.2 (100), 107.2 (10), 77.2 (21.8).

*1-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (**3r**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.9 Hz, 2H), 7.60 (d, J = 1.8 Hz, 1H), 7.49 (dd, J = 8.4, 1.9 Hz, 1H), 6.97 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 3.96 (s, 6H), 3.89 (s, 3H). GC MS (EI) $m\backslash z$ (relative intensity): 300.1 (M^+, 0.1), 165.1 (100), 135.1 (72.8), 107.1 (14.9), 77.1 (30), 64.1 (10.3).

*1-(Naphthalen-2-yl)-2-(p-tolyl)ethane-1,2-dione (**3s**).*[13g] Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.97−7.88 (m, 4H), 7.78 (d, J = 8.1 Hz, 2H), 7.63−7.52 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H). GC MS (EI) $m\backslash z$ (relative intensity): 274.3 (M^+, 0.1), 246.3 (87.1), 231.3 (28.6), 207.2 (7.95), 155.2 (89.2), 126.2 (16.2), 119.2 (100), 77.2 (10.3), 65.2 (17.9).

*1-(4-Methoxyphenyl)-2-(naphthalen-2-yl)ethane-1,2-dione (**3t**).* Off white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.10 (dd, J = 8.6, 1.6 Hz, 1H), 8.03−7.87 (m, 5H), 7.67−7.61 (m, 1H), 7.56 (dd, J = 11.1, 4.0 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H). GC MS (EI) $m\backslash z$ (relative intensity): 290.3 (M^+, 0), 155.2 (26.1), 135.2 (100), 126.3 (15.3), 107.2 (13.6), 77.2 (21.2), 40.1 (12.4).

*1-(4-Bromophenyl)-2-(1H-indol-3-yl)ethane-1,2-dione (**3u**).*[13h] White solid; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.45 (s, 1H), 8.23−8.21 (m, 2H), 7.90 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.58−7.56 (m, 1H), 7.35−7.30 (m, 2H); LC−MS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{11}BrNO_2$, 327.1; found, 327.1, HRMS (TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{11}BrNO_2$, 327.9968; found, 327.9973.

*1-(1-Methyl-1H-indol-3-yl)-2-phenylethane-1,2-dione (**3v**).*[13h] White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (s, 1H), 8.10 (t, J = 6.8 Hz, 2H), 7.80 (s, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.40−7.38 (m,3H), 3.82 (s, 3H); LC−MS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{14}NO_2$, 264.1; found, 264.1.

*1-(4-Chlorophenyl)-2-(1H-pyrrol-3-yl)ethane-1,2-dione (**3w**).*[13h] Yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.95 (s, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 7.05 (s, 1H), 6.38 (t, J = 1.6 Hz, 1H); LC−MS (ESI) m/z [M + H]$^+$ calcd for $C_{12}H_9ClNO_2$, 234; found, 234. HRMS (TOF) m/z [M + H]$^+$ calcd for $C_{12}H_9ClNO_2$, 234.0316; found, 234.0327.

*1-(3-Methoxyphenyl)-2-(1-methyl-1H-pyrrol-3-yl)ethane-1,2-dione (**3x**).*[13h] Yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, J = 8.4 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.10 (dd, J = 1.6, 8.4 Hz, 1H), 6.91 (s, 1H), 6.78 (m,1H), 6.11 (dd, J = 2.4, 4.0 Hz, 1H), 4.00 (s, 3H), 3.78 (s, 3H); LC−MS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{14}NO_3$, 244; found, 244. HRMS (TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{14}NO_3$, 244.0968; found, 244.0972.

*1-(4-Bromophenyl)-2-(thiophen-3-yl)ethane-1,2-dione (**3y**).* Yellow solid (201 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 2.8, 1.2 Hz, 1H), 7.93−7.83 (m, 2H), 7.70−7.62 (m, 3H), 7.41 (dd, J = 5.1, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.91, 186.39, 137.74, 137.34, 137.25, 132.31, 131.50, 130.42, 127.33, 127.15; GC MS (EI) $m\backslash z$ (relative intensity): 294.0 (M^+, 2.6), 183.1 (25), 155.2 (11), 111.2 (100), 83.0 (8.4).

*1-(4-Methoxyphenyl)-2-(thiophen-2-yl)ethane-1,2-dione (**3z**).* Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.00 (m, 2H), 7.84−7.79 (m, 2H), 7.18 (dd, J = 4.8, 4.0 Hz, 1H), 7.00−6.96 (m, 2H), 3.89 (s, 3H). GC MS (EI) $m\backslash z$ (relative intensity): 246 (M^+,0), 135.2 (100), 92.2 (17.4), 77.2 (19.1), 64.2 (8.9), 40.1 (24.6).

*Biphenyl (**4a**).*[13i] White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63−7.60 (m, 4H), 7.48−7.44 (m, 4H), 7.39−7.35 (m, 2H).

*2-Hydroxy-1,2-diphenylethan-1-one (**5a**).*[13j] Off white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, J = 5.2, 3.4 Hz, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.7 Hz, 2H), 7.36−7.25 (m, 5H), 5.95 (d, J = 6.1 Hz, 1H), 4.56 (d, J = 6.1 Hz, 1H). GC MS (EI) $m\backslash z$ (relative intensity): 212.1 (M^+,0), 165.3 (1.7), 105.3 (100), 77.3 (54.1), 63.2 (1.3), 51.3 (12.3).

*2-Hydroxy-2-(4-methoxyphenyl)-1-(p-tolyl)ethan-1-one (**5b**).* Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 2.1 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 1H), 2.43 (s, 3H). GC MS (EI) $m\backslash z$ (relative intensity): 246 (M^+,0), 135.2 (100), 92.2 (17.4), 77.2 (19.1), 64.2 (8.9), 40.1 (24.6).

*Diphenylmethanol (**7a**).* Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (ddd, J = 12.7, 8.0, 3.6 Hz, 8H), 7.26 (ddd, J = 7.2, 3.0, 1.4 Hz, 2H), 5.84 (d, J = 2.2 Hz, 1H), 2.23 (d, J = 3.0 Hz, 1H). GC MS (EI) $m\backslash z$ (relative intensity): 184. (M^+,0), 165.2 (12.5), 152.2 (5.4), 105.2 (100), 77.2 (47), 51.2 (12.7).

*Benzophenone (**8a**).* Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83−7.79 (m, 4H), 7.59 (t, J = 7.4 Hz, 2H), 7.48 (t, J = 7.6 Hz, 4H). GC MS (EI) $m\backslash z$ (relative intensity): 182.2 (M^+,0), 152.2 (4.1), 105.2 (100), 77.2 (55.5), 51.2 (16.9).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06031.

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All experimental procedures, characterization data, and spectra of all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Satyanarayana Battula − *Tarsadia Institute of Chemical Sciences, Uka Tarsadia University, Bardoli, Gujarat 394350, India;* orcid.org/0000-0002-0540-8844; Email: satyamssd@gmail.com

Authors

Aman A. Desai − *Aether Industries Pvt. Ltd., Surat, Gujarat 394230, India*

Jigar Y. Soni − *Department of Chemistry, Madhav University, Sirohi, Rajasthan 307026, India;* orcid.org/0000-0002-9779-6054

Dhruv P. Mehta − *Aether Industries Pvt. Ltd., Surat, Gujarat 394230, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c06031

Notes

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